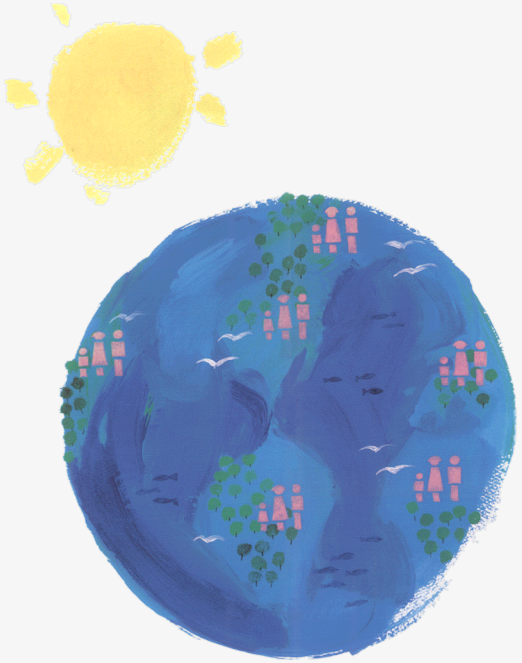
NICEATM

National Toxicology Program
Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



ICCVAM Test Method Evaluation Process and Charge to the Expert Panel

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ICCVAM *In Vitro* Acute Toxicity Peer Panel Evaluation

May 23, 2006
National Institutes of Health
Bethesda, Maryland

National Toxicology Program

NIEHS

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

ICCVAM Peer Review Panel Meeting

- May 23, 2006, NIH, Bethesda,Maryland
- Scientific Panel
  - 16 scientists
  - 6 countries
- Purpose: Evaluate the validation status of two in vitro cytotoxicity test methods proposed for estimating starting doses for in vivo acute oral toxicity testing
  - To reduce and refine animal use

The 15 ICCVAM Agencies

Regulatory/Research

Consumer Product Safety Commission

Department of Agriculture

Department of the Interior

Department of Transportation

Environmental Protection Agency

Food and Drug Administration

Occupational Safety and Health Administration

Non-Regulatory/Research

Agency for Toxic Substances and Disease Registry

Department of Defense

Department of Energy

National Cancer Institute

National Institute of Environmental Health Sciences

National Institute for Occupational Safety and Health

National Library of Medicine

National Institutes of Health

History of ICCVAM

1994 *ad hoc* ICCVAM established
- Develop criteria for validation and regulatory acceptance of test methods
- Develop a process to achieve regulatory acceptance of scientifically validated methods

1997 Final report of the *ad hoc* ICCVAM

1997 ICCVAM established
- Replaced *ad hoc* ICCVAM
- Implemented NIEHS directives: P.L. 103-43

1998 NICEATM established

2000 ICCVAM Authorization Act of 2000: P.L. 106-545
- Established “permanent” ICCVAM

2003 Revised ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods published

Preamble: ICCVAM Authorization Act (P.L. 106-545)

"To establish, where feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that

- *protect human and animal health and the environment*
- *while reducing, refining, or replacing animal tests and*
- *ensuring human safety and product effectiveness."*

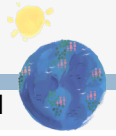
Purposes of ICCVAM (P.L. 106-545)[1]

- Increase efficiency and effectiveness of Federal agency test method review
- Eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies
- Optimize utilization of scientific expertise outside the Federal government
- Ensure that new and revised test methods are validated to meet the needs of Federal agencies
- Reduce, refine, or replace the use of animals in testing, where feasible

[1]Section 463A(b) of the Public Health Services Act (NIEHS), 42 U.S.C. § 285*l*-1(b)

ICCVAM Duties (P.L. 106-545)

- Facilitate and provide guidance on test method development, validation criteria, and validation processes
- Consider petitions from the public for review and evaluation of validated test methods
- Facilitate acceptance of scientifically valid test methods
- Review and evaluate new or revised or alternative test methods applicable to regulatory testing
- Submit test recommendations to Federal agencies
- Facilitate interagency and international harmonization of test methods



NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

- Located at NIEHS
- Functions:
  - Administer ICCVAM
  - Provide scientific and operational support for ICCVAM activities
  - Organize test method peer reviews, expert panel meetings, and workshops
  - Communicate and partner with stakeholders
  - Conduct independent validation studies

- http://iccvam.niehs.nih.gov

What is Validation?

- **A determination of the usefulness and limitations of a test method for a specific purpose[1]**
- **The process by which the *reliability* and *relevance* of a procedure are established for a specific purpose.[1]**
  - ***Reliability:*** A measure of the extent to which a test method can be performed reproducibly within and among laboratories over time.
    - Assessed by calculating intra- and inter-laboratory reproducibility and intra-laboratory repeatability.
  - ***Relevance:*** The extent to which a test method correctly predicts or measures the biological effect of interest.
    - Relevance incorporates consideration of the 'accuracy' or 'concordance' of a test method.
- ***Adequate validation is a prerequisite for regulatory acceptance consideration***

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[1] ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods; NIH Pub. No. 03-4508, 2003, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/subguide.htm

Criteria for Test Method Validation[1]

1. Clear statement of proposed use
2. Biological basis/relationship to effect of interest
3. Formal detailed protocol
4. Reliability assessed
5. Relevance assessed
6. Limitations described
7. All data available for review
8. Data quality: *Ideally GLPs*
9. Independent scientific peer review

[1]Adopted from: Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf

Criteria for Test Method Acceptance[1]

1. Fits into the regulatory testing structure
2. Adequately predicts the toxic endpoint of interest
3. Generates data useful for risk assessment
4. Adequate data available for specified uses
5. Robust and transferable
6. Time and cost-effective
7. Adequate animal welfare consideration (3Rs)

[1]Adopted from: Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods; NIH Pub. No. 97-3981, 1997, NIEHS, Research Triangle Park, NC. http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf

Why acute toxicity testing?

- To evaluate and classify the hazard potential of acute single exposures to substances
  - Used to label the hazard of chemicals and products
  - Basis for child-proof container lids

- Poisoning is a serious public health problem
  - 4 million poisoning events annually in the U.S.[1].
  - 30,800 poisoning deaths in 2001
    - Second leading cause of injury-related death behind automobile accidents (42,433 deaths)[1].

[1]Institute of Medicine. 2004. Forging a Poison Prevention and Control System. Washington: National Academies Press.

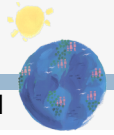
International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity

- October 17-20, 2000 in Arlington, VA;
  - Organized by ICCVAM and NICEATM
- Co-sponsors:
  - National Institute for Environmental Health Sciences (NIEHS)
  - National Toxicology Program (NTP)
  - U.S. Environmental Protection Agency (EPA)
- Workshop objectives
  - Evaluate current validation status of *in vitro* test methods for predicting acute oral toxicity
  - Identify research, development, and validation efforts that might further enhance the use of *in vitro* methods to assess acute systemic toxicity

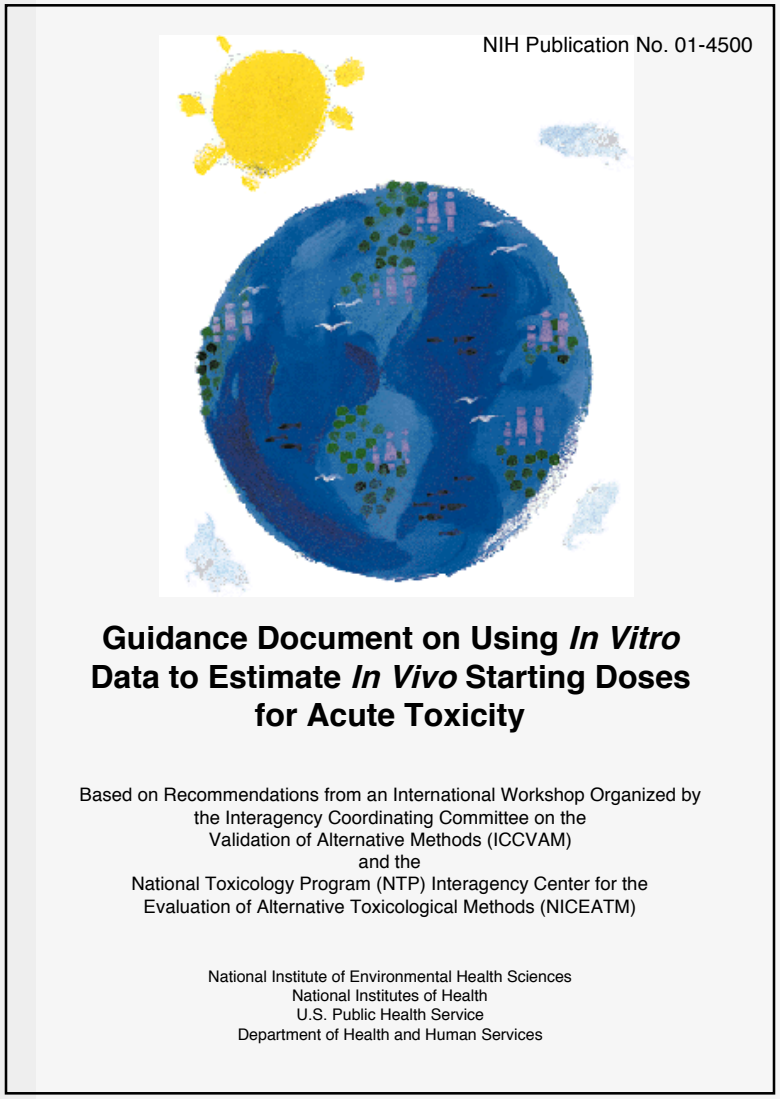
International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity

- Workshop and ICCVAM recommendations:
  - Short-term:
    - Goal:
      - **Reduce** animal use for acute systemic toxicity assays with *in vitro* methods to estimate starting doses[1]
    - Approach:
      - Standardization and validation of two cytotoxicity assays: one using a human cell system and one using a rodent cell system
  - Long-term:
    - Goal:
      - **Replace** animal use with *in vitro* methods that predict human acute systemic toxicity using human cells and tissues
    - Approach:
      - Support research needed to develop the additional components for a battery of in vitro tests necessary to accurately predict hazard classification categories

[1]Spielmann H, Genschow E, Liebsch M, Halle W. 1999. Determination of the starting dose for acute oral toxicity (LD_{50}) testing in the up and down procedure (UDP) from cytotoxicity data. Altern Lab Anim. **27**:957-966.



Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity



- Published in September 2001
- Described how to use *in vitro* IC_{50} cytotoxicity data to estimate starting doses for animal studies for acute systemic toxicity tests
- Provided protocols for 2 basal cytotoxicity methods
  - Neutral red uptake (NRU)
    - 3T3 mouse fibroblasts
    - Normal human keratinocytes
- Supported by studies in one lab on 11 chemicals (IIVS)
- Available at http://iccvam.niehs.nih.gov

ICCVAM
NICEATM

ICCVAM 2001 Recommendations: Research and Development to Advance *In Vitro* Tests for Acute Toxicity

- Endorsed October 2000 Workshop recommendations to develop the in vitro systems necessary to predict acute toxicity in addition to basal cytotoxicity
  - Target organ toxicity
  - Methods to predict ADME

- ECVAM A-Cute-Tox Project
  - Coordinated by ECVAM
  - Goal: To develop and validate an in vitro strategy to replace animals for acute oral toxicity testing
  - Addresses the R&D recommendations from the 2000 ICCVAM Workshop
  - Initiated: January 2005.
  - Completion: January 2010.

NICEATM-ECVAM Independent Validation Study on *In Vitro* Methods for Assessing Acute Systemic Toxicity

- Oct 2000 International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity
- Sep 2001 Publication of Workshop Report and *Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses*
- Oct 2001 NICEATM and ECVAM begin planning of validation study
- Aug 2002 Validation study initiated
- Jan 2005 Validation Study completed
- Mar 2006 Draft documents released to the peer panel and public
- May 2006 Peer Review Meeting

Charge to the Peer Panel

- Review the *In Vitro* Acute Toxicity Test Methods Draft Background Review Document (BRD) for completeness and for any errors or omissions
- Evaluate the extent to which each of the applicable criteria for validation and acceptance have been adequately addressed for the test methods and their specific proposed use
- Comment on the extent to which the draft ICCVAM test method recommendations are supported by the information provided in the draft Background Review Document
  - Proposed test method uses
  - Proposed recommended standardized protocols
  - Proposed test method performance standards
  - Proposed future studies

ICCVAM *In Vitro* Acute Toxicity Peer Panel

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